

Inhalant Abuse: Supporting Broad-Based Research Approaches

The National Institute on Drug Abuse (NIDA) seeks to broaden the understanding of all aspects of inhalant abuse (i.e., from epidemiology, to treatment, to the underlying neurobiological mechanisms). Prevalence data from both the National Household Survey (NHS) and Monitoring the Future Survey (MTF) indicate that inhalant abuse continues to be a major public health concern among grade school children, adolescents, and some adults. According to the 2004 MTF Survey, inhalants stand out in stark contrast to the progress made in reducing overall drug use among children and adolescents. Inhalants pose a particularly significant problem since they are readily accessible, legal, and inexpensive. These features mean that they tend to be abused by younger children, in whom their highly toxic effects can be even more lethal than in adults. Furthermore, MTF lifetime prevalence figures indicate that the percentage of students who have tried inhalants remains at high levels. The NHS indicates that lifetime use of inhalants is greater than lifetime use of crack cocaine or heroin. Given the paucity of research on all aspects of inhalant abuse, this announcement is designed to encourage broad-based research that has the potential for informing prevention and treatment interventions for inhalant abuse, particularly for children and adolescents. Basic epidemiological, behavioral, cognitive and neurobiological research is needed across children and adolescent populations, as are animal models of preadolescents and adolescents, to determine the antecedent variables (e.g., impaired decision-making processes, impulsivity), consequences (e.g., neurological and physiological disorders, accidents, dropping out of school, impairments resulting from prenatal exposure, and cognitive deficits), and the underlying mechanisms associated with or resulting from inhalant exposure.

Inhalants are volatile substances that produce chemical vapors that can be inhaled to induce a psychoactive or mind-altering effect. Several subcategories of inhalants have been identified, including: 1) industrial or household products (e.g., paint thinners or solvents, degreasers or cleaning fluids, gasoline, and volatile substances in glues); 2) art and office supply solvents (e.g., correction fluids, glues, and solvents in magic markers); 3) gases such as butane and chlorofluorocarbons used in household or commercial products (e.g., butane lighters, whipped cream dispensers [nitrous oxide], electronic contact cleaners [dusters] and refrigerant gases); 4) household aerosol propellants used in items such as hair, cooking, lubricant and fabric protector sprays; 5) medical anesthetic gases such as ether, chloroform, halothane, and nitrous oxide; and 6) aliphatic nitrites.

Inhalants are appealing for a variety of reasons: They are relatively inexpensive, can be purchased legally, and are readily accessible to most everyone including those most likely to abuse them—children and adolescents. Moreover, the “high” from inhalants onsets and disappears quickly, in comparison to other drugs of abuse. The practices of “sniffing,” “huffing,” “bagging,” or inhaling to get high are various forms of inhalation abuse popular among users. Disorders associated with inhalant abuse include toluene-induced hearing loss, cerebellar ataxia, sensory-motor polyneuropathy resulting from nitrous oxide exposure, hexane (e.g., methylethylketone) induced peripheral neuropathy, distal-renal acidosis, and cardiac arrhythmias.

Prenatal exposure to inhalants can have adverse consequences, and research is needed to determine their short- and long-term effects on infant development. Deaths have been attributed to inhalant abuse,

primarily resulting from anoxia and inhalant-abuse-related accidents. While some of these disorders have been studied and documented, further study is needed to understand the underlying mechanisms of these disorders and the development of interventions to treat these conditions. Additional research is also needed to characterize addiction to inhalants and to compare the abuse of inhalants with abuse of other substances, such as sedatives and alcohol. Insofar as inhalant abuse is an international public health concern, epidemiological research should examine regional and cultural differences in the pattern of use and substances abused among various populations. Treatment and prevention interventions for inhalant abuse should consider regional differences and other variables in the development and testing of new interventions. Additional research, therefore, is needed to address all aspects of inhalant abuse, including the epidemiology, the behavioral, cognitive, and neurobiological antecedents and consequences of inhalant abuse, as well as the treatment and prevention of inhalant abuse. Specific research topics that would be appropriate for this initiative are described below. For further information about inhalant abuse and this area of research, please refer to: *Inhalant Abuse: A Volatile Research Agenda*, NIDA Monograph 129, 1992; Sharp and Rosenberg, *Inhalants*; and “Substance Abuse, a Comprehensive Textbook,” 3rd ed. pp. 246–264, 1997; Balster, R., *Neural Basis of Inhalant Abuse*. *Drug and Alcohol Dependence*, 51: 207–214, 1998.

Research is needed to characterize the nature and extent of the inhalant abuse for different classes of abused inhalants in relevant population subgroups. Studies are needed on the initiation, experimentation, development, and cessation of inhalant abuse and the consequences of abuse of different classes of solvents and gases. Inhalant abuse is widespread and affects diverse groups in domestic and international populations. Because of this diversity, studies should consider sociocultural, socioeconomic, gender, and regional differences, as well as factors associated with risk, vulnerability, protection, and resiliency to inhalant abuse and its consequences. Research is needed to determine how family support, role models, the extended family, pre-existing conditions (e.g., HIV/AIDS, mental health disorders, alcohol and other substance abuse), peer groups and socioeconomic status affect initiation, continuation, escalation, and cessation of inhalant use. Data are needed on the incidence, prevalence, and trends in abuse of inhalants and on the health consequences (e.g., other drug use, sexually transmitted infections, including HIV/AIDS) as well as the behavioral and social consequences (e.g., automobile accidents, school dropout) associated with inhalant abuse. Further research of interest includes, but is not limited to the following studies: 1) Characterize the nature and extent of abuse of inhalants among youth and adolescents in different regions of the nation or world (e.g., rural, suburban, and urban areas), across culturally or geographically distinct communities (e.g., communities along the United States–Mexico border), and among diverse ethnic, socioeconomic, and occupational groups. 2) Characterize trajectories in inhalant abuse, from grade school to early adolescence and young adulthood (i.e., initiation, progression, maintenance, and cessation). 3) Understand the patterns, incidence, and prevalence of inhalant use among youth at risk, such as school dropouts, gang members, children of drug users, and homeless youth. 4) Examine diverse social circumstances and interactions of youth, such as peer networks and subcultures, family dynamics, community context, and communication technology (e.g., the Internet) and how they may impact epidemiologic patterns and trends in

inhalant abuse and in the progression of other substance abuse. 5) Determine reasons for inhalant use, attitudes and perceived risks of use, knowledge of potential short- and long-term consequences of use (e.g., accidents due to inhalant intoxication, health effects such as CNS toxicity) and reasons for continued use or cessation of use. 6) Characterize developmental trends in inhalant abuse, including potential cohort, secular, and intergenerational trends in the epidemiology of use. 7) Identify etiological factors associated with inhalant use and abuse, including potential predispositional risk factors (e.g., comorbidity, psychiatric disorders and other emotional, physical, and psychosocial stressors) and vulnerabilities associated with gender, age, ethnicity, and socioeconomic status. 8) Determine progressive behavioral, social, and health consequences of long-term inhalant abuse, such as morbidity and mortality, criminal activity, deviancy in school, familial conflicts and abuse, and problems in employability and job performance. 9) Explore the relationship between inhalant abuse and use and abuse of alcohol and other drugs. To what extent and for whom does availability of alcohol and other drugs lead to decreased inhalant abuse? Do some inhalant users continue to use and abuse inhalants despite availability of other drugs and alcohol, and if so, why? 10) Assess and compare the incidence and prevalence of abuse and abuse of particular inhalants in different countries and regions of the world to understand unique determinants, correlates, and consequences of inhalant abuse, and to identify opportunities for rapid, targeted preventive interventions.

Inhalants are widely abused by youngsters due to their easy accessibility through household products as well as their low cost. Unfortunately, inhalant abuse poses definite dangers to the health of young children, including cognitive, neurological and physiological disorders, as well as the threat of sudden death. Inhalant abuse is often associated with behavioral problems such as dropping out of school, delinquency, and crime in young people. In fact, inhalants are considered to be the precursors to later substance abuse and related psychosocial problems.

Current inhalant prevention strategies focus on increasing young people’s awareness and information regarding the dangers of inhalant abuse. Since the average age of inhalant initiation is relatively young, prevention strategies should target not only young people but their parents and teachers as well. Therefore, inhalant abuse prevention strategies should be multicomponent and comprehensive, and include family-based and school-based components.

Prevention programs should begin in the primary grades where many young people’s beliefs and attitudes about drug use are formed. However, care must be exercised in developing interventions that avoid unnecessary sensitization of youth to the issue of inhalant abuse in order to avoid unintended consequences. In fact, media and public information interventions must be developed according to guidelines, which on one hand reduce unnecessary sensitization of youth to the presence of inhalants in certain materials, and on the other hand educate youth, parents, teachers, and other adults about the hazards of inhalants. Inhalant prevention strategies should include comprehensive approaches that meld carefully constructed and developmentally appropriate media, training, technical assistance, information dissemination, and local community action efforts.

The field of prevention research should develop a scientifically sound knowledge base concerning the efficacy and effectiveness of existing inhalant abuse prevention strategies and policies, as well as develop and test innovative intervention strategies.

The development of sex-based prevention interventions are needed that are based on the differential etiologic factors found in males and females. The following are examples of research topics that address important gaps in our knowledge of inhalant prevention: 1) Develop and test the efficacy and effectiveness of inhalant prevention strategies for youth at high-risk for inhalant abuse in different cultural (e.g., Hispanics, Native Americans, etc.), geographic (e.g., urban, rural, etc.), and socioeconomic (e.g., poor, affluent) settings; 2) develop population- or context-specific universal, selective, and/or indicated prevention approaches that can be implemented and administered easily, efficiently, and at low cost; 3) compare and contrast the efficacy and effectiveness of family-based, school-based, and multiple-component prevention strategies; 4) develop and test the efficacy and effectiveness of age-specific inhalant prevention strategies.

There is a paucity of research on the behavioral or pharmacotherapeutic approaches to treatment of inhalant abusers. Inhalant abusers are often excluded from studies on drug abusers, and there have been no NIDA-funded studies focusing exclusively on treating inhalant abusers. Research is needed on behavioral treatments focusing on different populations of inhalant abusers. Stage I or early behavioral treatment development research focusing on the development, refinement, and pilot testing of behavioral interventions are also encouraged under this RFA. For a description of Stage I research, please see PA-99-107, A Behavioral Therapies Development Program at: <http://grants.nih.gov/grants/guide/pa-files/PA-99-107.html>.

This includes research that seeks to develop new therapeutic approaches, or refine or modify existing behavioral or psychosocial therapeutic approaches (e.g., forms of cognitive-behavioral therapy, family therapy, motivational enhancement, drug counseling, group therapy, motivational incentives, etc.). Stage I also involves the pilot testing of these therapies. Pilot testing that seeks to clarify the mechanisms by which behavioral treatments produce change in inhalant use, including identification of mediators and moderators that influence abuse of inhalants and other drugs, is encouraged. Such pilot testing may utilize a variety of designs, including but not limited to single-case designs, dismantling, additive, and nonparametric designs, where appropriate. Specific areas of Stage I interest include but are not limited to 1) stage I research that addresses the unique characteristics and problems of specific populations of inhalant abusers, including but not limited to young male and female adolescents, women, men who have sex with men, individuals with HIV/AIDS, persons in professions with extended exposure to inhalants, individuals with comorbid mental or physical disorders, chemically dependent pregnant women, adolescents who are abusing another drug or multiple other drugs, adolescents living in impoverished areas, individuals in the criminal justice system, or other populations abusing inhalants. This research may include the development of treatment modules that address the unique characteristics of particular populations of inhalant abusers and integration of these modules into other therapeutic approaches; 2) development and pilot testing of treatments for specific populations of inhalant abusers based upon recent advancements in the behavioral, social, or cognitive sciences. Where appropriate, outcome measures may include, in addition to measures of substance abuse, other measures of functioning (e.g., behavioral, social, etc.) and also measurements of brain functioning (e.g., MRI, PET-scan, etc.); 3) development and pilot testing of behavioral treatments tailored to people who have

inhalant-related cognitive impairments; this may include research that focuses on behavioral therapies aimed at cognitive rehabilitation, based upon recent advancements and theories in cognitive neuroscience, and also may include measurements of changes in brain function associated with therapeutic intervention; 4) development and pilot testing of behavioral treatments that have a particular focus on the initial stage of treatment engagement, including the development of "treatment modules" that can be incorporated into other therapeutic approaches to improve engagement and retention; 5) development and pilot testing of brief behavioral treatment interventions (e.g., for use in primary care settings). 6) Other studies should identify preexisting and co-existing neurobiological, psychosocial, and environmental factors that significantly impact treatment outcomes; 7) determine and examine the physiology of withdrawal from inhalants, including the study of potential treatments to ameliorate any withdrawal syndrome and determine if different classes of inhalants induce different withdrawal syndromes; 8) develop and improve methods for diagnosing, treating, and increasing physician awareness of inhalant abuse, overdose, and poisoning, including research aimed at developing and improving analyses for inhalants that can be used in medical emergency care or other settings; 9) develop and/or test medications currently used or under development for other drug dependencies (e.g., alcohol, sedatives).

Several medical sequelae have been associated with inhalant abuse, including hearing loss, neurological degeneration, metabolic acidosis, loss of cerebellar function, and cardiac arrhythmia. Additional research is needed to determine and characterize the neuropsychological, cognitive, behavioral, cellular, and physiological consequences of inhalant abuse using clinical, animal, and *in vitro* investigations. Additional research is needed to develop possible pharmacotherapies to treat the medical and other related conditions associated with inhalant abuse including addiction.

Models of inhalant abuse and addiction should take into account the fact that inhalant abuse occurs among children and adolescents. The models should also focus on the pattern of use and how inhalants are abused. When appropriate, investigators should measure and model acute and long-term administration of solvent/gas mixtures, their pharmacodynamic properties, and the bioavailability of abused solvents and their metabolites.

Examples of appropriate research topics and approaches include but are not limited to the following: 1) study of the cellular and systemic changes (e.g., measures of central neurotransmitter systems, renal metabolic processes, cobalamin systems related to N₂O) involved in single and repeated inhalant exposure; 2) determination of the mechanisms of the acute and long-term toxic effects of inhalants on, for example, central nervous, cardiovascular, renal, pulmonary, and immune systems. Research could focus on known inhalant-induced toxicities (e.g., high-frequency hearing loss, renal acidosis, cerebellar ataxia); 3) characterization of the acute subjective, reinforcing and cognitive effects of inhalant abuse and their underlying neural mechanisms; 4) correlation between the pharmacokinetic and pharmacodynamic properties of inhalants and their behavioral, cognitive, and/or physiologically toxic effects; 5) comparison of the behavioral, cognitive, and neurobiological effects of different types of inhalants with each other or with other abused substances (e.g., alcohol, benzodiazepines, dissociative anesthetics or sedatives), focusing on understanding the systems involved and the basic underlying mechanisms; 6) characterization of the relative abuse potential of inhalant compounds

using innovative determinations of these substances and their classification; 7) study of tolerance and/or sensitization to inhalants and determine the underlying neurobiological mechanisms associated with these phenomena; 8) development of animal models to study motivational processes, and the environmental and genetic factors that influence the acquisition and maintenance of inhalant self-administration; 9) identification of the consequences of acute and chronic inhalant administration on sensory/perceptual, motor, behavioral, and cognitive processes in known abusers or with the use of appropriate animal models; study of cognition in inhalant abusers employing longitudinal or prospective designs; 10) study of the short- and long-term developmental consequences of prenatal exposure to inhalants. Possible ontogenetic consequences of inhalant exposure could be examined at various stages of development using animal models or in people exposed perinatally to inhalants; determination of the nature and characteristics of a possible Fetal Solvent Syndrome (FSS); 11) study of potential neurotoxic effects of inhalants in humans (and animals) using neuroimaging techniques and by using postmortem tissue analyses; 12) use of neuroimaging techniques (i.e., PET, fMRI, and other technologies) to relate neural integrity and changes in metabolic function with patterns of inhalant use and/or prior abuse; 13) study of the etiology, diagnosis, progression, and treatment of HIV/AIDS in inhalant abusers, as well as complications associated with HIV therapy for inhalant users (e.g., drug-drug interactions); 14) study of the short- and long-term consequences of regular inhalant abuse as a function of age or developmental period (e.g., adolescence).

This funding opportunity will use the NIH Research Project Grant (R01), Small Grant (R03), and the Exploratory/Developmental Grant (R21) award mechanism(s). As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This funding opportunity uses just-in-time concepts. It also uses the modular as well as the non-modular budget formats (see <http://grants.nih.gov/grants/funding/modular/modular.htm>). Specifically, if you are submitting an application with direct costs in each year of \$250,000 or less, use the modular budget format described in the PHS 398 application instructions, available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. Otherwise, follow the instructions for nonmodular research grant applications. For further assistance contact GrantsInfo, 301-435-0714, (telecommunications for the hearing impaired: TTY 301-451-0088), or by e-mail: GrantsInfo@nih.gov.

Applications must be prepared using the most current PHS 398 research grant application instructions and forms. Applications must have a D&B Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling 866-705-5711 or through the web site at <http://www.dnb.com/us/>. The D&B number should be entered on line 11 of the face page of the PHS 398 form. For key dates related to this announcement see <http://grants.nih.gov/grants/funding/submissionschedule/htm>.

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